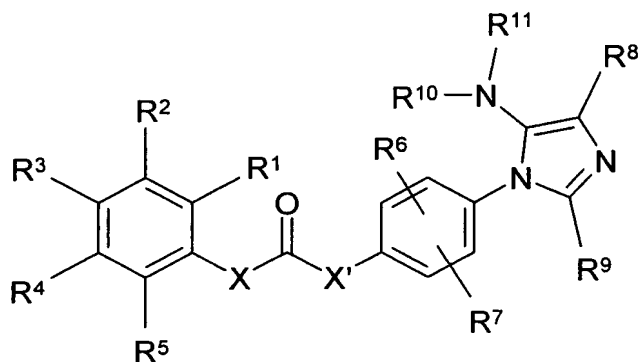


Patent Claims

1. Compounds of the formula I

5

10



I

15

in which

 $R^1, R^2, R^3,$ R^4, R^5

each, independently of one another, denote H, A, OH, OA, alkenyl, alkynyl, NO_2 , NH_2 , NHA, NA_2 , Hal, CN, COOH, COOA, -OHet, -O-alkylene-Het, -O-alkylene- $\text{NR}^{10}\text{R}^{11}$ or $\text{CONR}^{10}\text{R}^{11}$,

20

two adjacent radicals selected from R^1, R^2, R^3, R^4, R^5

together also denote -O- CH_2 - CH_2 -, -O- CH_2 -O- or -O- CH_2 - CH_2 -O-,

25

 R^6, R^7

each, independently of one another, denote H, A, Hal, OH, OA or CN,

 R^8

denotes CN, COOH, COOA, CONH_2 , CONHA or CONA_2 ,

30

 R^9

denotes H or A,

 R^{10}, R^{11}

each, independently of one another, denote H or A,

Het

denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubsti-

35

tuted by Hal, A, OA, COOA, CN and/or carbonyl oxygen (=O),

A denotes alkyl having 1 to 10 C atoms, where, in addition, 1-7 H atoms may be replaced by F and/or chlorine,
5 X, X' each, independently of one another, denote NH or are absent,

Hal denotes F, Cl, Br or I,
and pharmaceutically usable derivatives, solvates, salts and stereo-
10 isomers thereof, including mixtures thereof in all ratios.

2. Compounds according to Claim 1 in which

X is absent or denotes NH,

15 X' denotes NH,

and pharmaceutically usable derivatives, solvates, salts and stereo-
isomers thereof, including mixtures thereof in all ratios.

3. Compounds according to Claim 1 or 2 in which

20 R¹, R², R³,

R⁴, R⁵ each, independently of one another, denote H, A, OH,
OA, NO₂, NH₂, NHA, NA₂, Hal, CN, -OHet,
-O-alkylene-Het or -O-alkylene-NR¹⁰R¹¹,

25 and pharmaceutically usable derivatives, solvates, salts and stereo-
isomers thereof, including mixtures thereof in all ratios.

4. Compounds according to one or more of Claims 1-3 in which

30 Het denotes a monocyclic saturated heterocycle having 1 to
3 N, O and/or S atoms, which is unsubstituted or may
be monosubstituted by COOA,

and pharmaceutically usable derivatives, solvates, salts and stereo-
35 isomers thereof, including mixtures thereof in all ratios.

5. Compounds according to one or more of Claims 1-4 in which

R^6, R^7 denote H,
and pharmaceutically usable derivatives, solvates, salts and stereo-
isomers thereof, including mixtures thereof in all ratios.

- 5 6. Compounds according to one or more of Claims 1-5 in which
 R^8 denotes CONH_2 or CN,
and pharmaceutically usable derivatives, solvates, salts and stereo-
isomers thereof, including mixtures thereof in all ratios.
- 10 7. Compounds according to one or more of Claims 1-6 in which
X is absent or denotes NH,
X' denotes NH,
15 $R^1, R^2, R^3,$
 R^4, R^5 each, independently of one another, denote H, A,
OH, OA, NO_2 , NH_2 , NHA, NA_2 , Hal, CN, -OHet,
-O-alkylene-Het or -O-alkylene- $\text{NR}^{10}\text{R}^{11}$,
20 Het denotes a monocyclic saturated heterocycle having 1
to 3 N, O and/or S atoms, which is unsubstituted or
may be monosubstituted by COOA,
 R^6, R^7 denote H,
 R^8 denotes CONH_2 or CN,
25 and pharmaceutically usable derivatives, solvates, salts and stereo-
isomers thereof, including mixtures thereof in all ratios.
- 30 8. Compounds according to one or more of Claims 1-7 in which
X is absent or denotes NH,
X' denotes NH,
 $R^1, R^2, R^3,$
 R^4, R^5 each, independently of one another, denote H, A, OH,
35 OA, NO_2 , NH_2 , NHA, NA_2 , Hal, CN, -OHet,
-O-alkylene-Het or -O-alkylene- $\text{NR}^{10}\text{R}^{11}$,
 R^6, R^7 denote H,

R^8 denotes CONH_2 or CN ,
 Het denotes piperidinyl, pyrrolidinyl, morpholinyl or piperazinyl, each of which is unsubstituted or monosubstituted by COOA ,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

9. Compounds according to one or more of Claims 1-8 in which

X, X' each, independently of one another, denote NH or is absent,

R^1, R^2, R^3, R^4, R^5 each, independently of one another, denote H , A , OH , OA , Hal , O-alkylene-Het or $-\text{O-alkylene-NR}^{10}\text{R}^{11}$,

R^6, R^7 denote H ,

R^8 denotes CONH_2 or CN ,

R^9 denotes H or A ,

R^{10}, R^{11} each, independently of one another, denote H or A ,

Het denotes piperidinyl, pyrrolidinyl, morpholinyl or piperazinyl, each of which is unsubstituted or monosubstituted by COOA ,

A denotes alkyl having 1 to 10 C atoms, where, in addition, 1-7 H atoms may be replaced by F and/or chlorine,

Hal denotes F, Cl, Br or I,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

10. Compounds according to Claim 1, selected from the group

1-[4-(5-amino-4-aminocarbonyl-1*H*-imidazol-1-yl)phenyl]-3-(2-methoxy-5-trifluoromethylphenyl)urea,

1-[4-(5-amino-4-aminocarbonyl-1*H*-imidazol-1-yl)phenyl]-3-(6-fluoro-3-trifluoromethylphenyl)urea,

1-[4-(5-amino-4-aminocarbonyl-1*H*-imidazol-1-yl)phenyl]-3-(4-fluoro-3-trifluoromethylphenyl)urea,

1-[4-(5-amino-4-aminocarbonyl-1*H*-imidazol-1-yl)phenyl]-3-(6-fluoro-3-methylphenyl)urea,

1-[4-(5-amino-4-aminocarbonyl-2-methyl-1*H*-imidazol-1-yl)-phenyl]-3-(6-fluoro-3-trifluoromethylphenyl)urea,

1-[4-(5-amino-4-aminocarbonyl-1*H*-imidazol-1-yl)phenyl]-3-(4-chloro-3-trifluoromethylphenyl)urea,

1-[4-(5-amino-4-aminocarbonyl-1*H*-imidazol-1-yl)phenyl]-3-(3-trifluoromethylphenyl)urea,

1-[4-(5-amino-4-aminocarbonyl-1*H*-imidazol-1-yl)phenyl]-3-(3-methylphenyl)urea,

1-[4-(5-amino-4-aminocarbonyl-1*H*-imidazol-1-yl)phenyl]-3-(4-chloro-6-methoxy-3-methylphenyl)urea,

1-[4-(5-amino-4-aminocarbonyl-1*H*-imidazol-1-yl)phenyl]-3-(5-fluoro-3-trifluoromethylphenyl)urea,

1-[4-(5-amino-4-aminocarbonyl-2-ethyl-1*H*-imidazol-1-yl)phenyl]-3-(6-fluoro-3-trifluoromethylphenyl)urea,

1-[4-(5-amino-4-aminocarbonyl-2-*tert*-butyl-1*H*-imidazol-1-yl)-phenyl]-3-(6-fluoro-3-trifluoromethylphenyl)urea,

1-[4-(5-dimethylamino-4-aminocarbonyl-1*H*-imidazol-1-yl)-phenyl]-3-(6-fluoro-3-trifluoromethylphenyl)urea,

1-[4-(5-amino-4-cyano-1*H*-imidazol-1-yl)phenyl]-3-(6-fluoro-3-trifluoromethylphenyl)urea,

1-[4-(5-amino-4-aminocarbonyl-1*H*-imidazol-1-yl)phenyl]-3-[6-(2-dimethylaminoethoxy)-3-trifluoromethylphenyl]urea,

1-[4-(5-amino-4-aminocarbonyl-1*H*-imidazol-1-yl)phenyl]-3-{6-[2-(morpholin-4-yl)ethoxy]-3-trifluoromethylphenyl}urea,

5-amino-1-[4-(2-fluoro-5-trifluoromethylbenzoylamino)phenyl]-
1*H*-imidazole-4-carboxamide,

5-amino-1-[4-(2-fluoro-5-trifluoromethylphenylcarbamoyl)-
phenyl]-1*H*-imidazole-4-carboxamide,

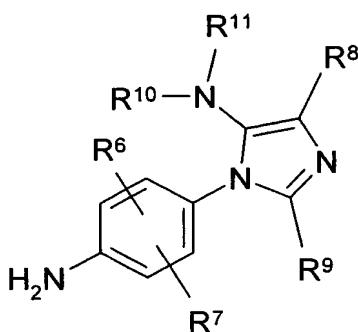
5-amino-1-[4-(2-fluoro-5-trifluoromethylbenzoylamino)phenyl]-
1*H*-imidazole-4-carboxamide,

and pharmaceutically usable derivatives, solvates, salts and stereo-
isomers thereof, including mixtures thereof in all ratios.

11. Process for the preparation of compounds of the formula I according
to Claims 1-10 and pharmaceutically usable derivatives, salts, sol-
vates and stereoisomers thereof, characterised in that

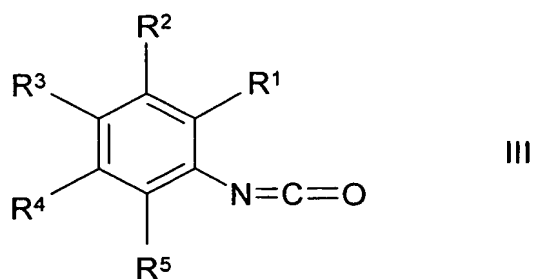
a) for the preparation of compounds of the formula I in which X, X'
denote NH,

a compound of the formula II



in which R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ have the meanings indicated in
Claim 1,

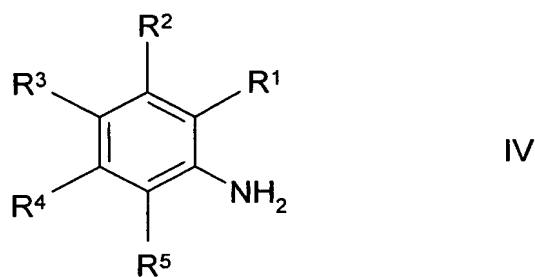
is reacted with a compound of the formula III



10 in which R^1 , R^2 , R^3 , R^4 and R^5 have the meanings indicated in Claim 1,

or

15 b) for the preparation of compounds of the formula I
in which X, X' denote NH,
a compound of the formula IV



in which R^1 , R^2 , R^3 , R^4 and R^5 have the meanings indicated in Claim 1,

30 is reacted with a chloroformate derivative to give an intermediate carbamate derivative,

which is subsequently reacted with a compound of the formula II,

or

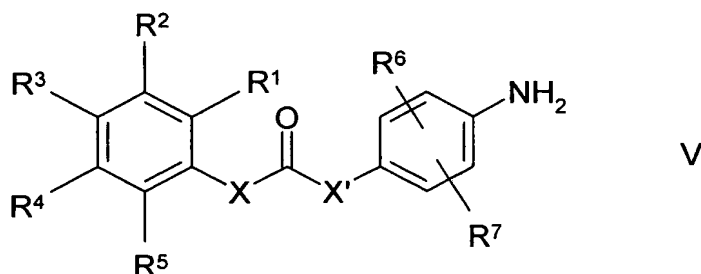
35 c) for the preparation of compounds of the formula I

in which

R^8 denotes CN, COOA, CONH₂, CONHA or CONA₂,

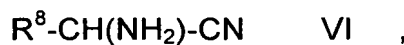
R^{10} , R^{11} denote H,

a compound of the formula V



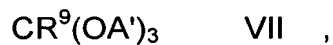
in which R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , X and X' have the meanings indicated in Claim 1,

is reacted with a compound of the formula VI



in which R^8 denotes CN, COOA, CONH₂, CONHA or CONA₂,

and with a compound of the formula VII



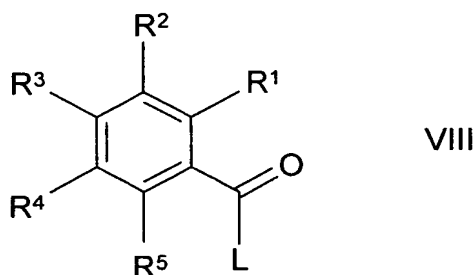
in which R^9 has the meaning indicated in Claim 1 and A' denotes alkyl having 1, 2, 3, 4, 5 or 6 C atoms,

or

d) for the preparation of compounds of the formula I

in which X is absent and X' denotes NH,

a compound of the formula II is reacted with a compound of the formula VIII



in which R^1 , R^2 , R^3 , R^4 and R^5 have the meanings indicated in Claim 1,

15 and L denotes Cl, Br, I or a free or reactively functionally modified OH group,

or

20 e) a compound of the formula I in which R^{10} , R^{11} denote H is converted by alkylation into a compound of the formula I in which R^{10} , R^{11} denote A,

25 and/or

a base or acid of the formula I is converted into one of its salts.

12. Medicaments comprising at least one compound of the formula I according to Claim 1 and/or pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.
- 30
13. Use of compounds according to Claim 1 and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios,
- 35

for the preparation of a medicament for the treatment of diseases in which the inhibition, regulation and/or modulation of kinase signal transduction plays a role.

- 5
14. Use according to Claim 13, where the kinases are selected from the group of the tyrosine kinases and Raf kinases.
- 10
15. Use according to Claim 14, where the tyrosine kinases are TIE-2, VEGFR, PDGFR, FGFR and/or FLT/KDR.
- 15
16. Use according to Claim 14 of compounds according to Claim 1, and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment of diseases which are influenced by inhibition of tyrosine kinases by the compounds according to Claim 1.
- 20
17. Use according to Claim 16 for the preparation of a medicament for the treatment of diseases which are influenced by inhibition of TIE-2, VEGFR, PDGFR, FGFR and/or FLT/KDR by the compounds according to Claim 1.
- 25
18. Use according to Claim 16 or 17, where the disease to be treated is a solid tumour.
- 30
19. Use according to Claim 18, where the solid tumour originates from the group of tumours of the squamous epithelium, the bladder, the stomach, the kidneys, of head and neck, the oesophagus, the cervix, the thyroid, the intestine, the liver, the brain, the prostate, the urogenital tract, the lymphatic system, the stomach, the larynx and/or the
- 35
- lung.

20. Use according to Claim 18, where the solid tumour originates from the group monocytic leukaemia, lung adenocarcinoma, small-cell lung carcinomas, pancreatic cancer, glioblastomas and breast carcinoma.
21. Use according to Claim 18, where the solid tumour originates from the group of lung adenocarcinoma, small-cell lung carcinomas, pancreatic cancer, glioblastomas, colon carcinoma and breast carcinoma.
22. Use according to Claim 16 or 17, where the disease to be treated is a tumour of the blood and immune system.
23. Use according to Claim 22, where the tumour originates from the group of acute myelotic leukaemia, chronic myelotic leukaemia, acute lymphatic leukaemia and/or chronic lymphatic leukaemia.
24. Use according to Claim 16 or 17 for the treatment of a disease in which angiogenesis is implicated.
25. Use according to Claim 24, where the disease is an ocular disease.
26. Use according to Claim 16 or 17 for the treatment of retinal vascularisation, diabetic retinopathy, age-induced macular degeneration and/or inflammatory diseases.
27. Use according to Claim 26, where the inflammatory disease originates from the group rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reaction.

28. Use according to Claim 16 or 17 for the treatment of bone pathologies, where the bone pathology originates from the group osteosarcoma, osteoarthritis and rickets.

5 29. Use of compounds of the formula I according to Claim 1 and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of solid tumours, where a therapeutically effective amount of a compound of the formula I is
10 administered in combination with a compound from the group 1) oestrogen receptor modulator, 2) androgen receptor modulator, 3) retinoid receptor modulator, 4) cytotoxic agent, 5) antiproliferative agent, 6) prenyl-protein transferase inhibitor, 7) HMG-CoA reductase inhibitor, 8) HIV protease inhibitor, 9) reverse transcriptase inhibitor and
15 10) further angiogenesis inhibitor.

30. Use of compounds of the formula I according to Claim 1 and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of solid tumours, where a therapeutically effective amount of a compound of the formula I is
20 administered in combination with radiotherapy and a compound from the group 1) oestrogen receptor modulator, 2) androgen receptor modulator, 3) retinoid receptor modulator, 4) cytotoxic agent, 5) antiproliferative agent, 6) prenyl-protein transferase inhibitor, 7) HMG-CoA reductase inhibitor, 8) HIV protease inhibitor, 9) reverse transcriptase inhibitor and 10) further angiogenesis inhibitor.

30 31. Use according to Claim 16 or 17 for the preparation of a medicament for the treatment of diseases which are based on disturbed TIE-2 activity,
35 where a therapeutically effective amount of a compound according to Claim 1 is administered in combination with a growth factor receptor inhibitor.

- 5 32. Use according to Claim 13 or 14 of compounds of the formula I for the preparation of a medicament for the treatment of diseases which are caused, mediated and/or propagated by Raf kinases.
33. Use according to Claim 32, where the Raf kinase is selected from the group consisting of A-Raf, B-Raf and Raf-1.
- 10 34. Use according to Claim 32, where the diseases are selected from the group of the hyperproliferative and non-hyperproliferative diseases.
35. Use according to Claim 32 or 34, where the disease is cancer.
- 15 36. Use according to Claim 32 or 34, where the disease is non-cancerous.
- 20 37. Use according to Claim 32, 34 or 36, where the non-cancerous diseases are selected from the group consisting of psoriasis, arthritis, inflammation, endometriosis, scarring, benign prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.
- 25 38. Use according to one of Claims 32, 34 or 35, where the diseases are selected from the group consisting of brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.
- 30
- 35